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14. ABSTRACT

Hand-held optical imaging devices using near-infrared (NIR) light are currently developed toward clinical translation of the technology. However, none of the devices developed to date have been used toward 3D tomography since they are not able to coregister the image to the tissue geometry. The objective for the work described herein is the clinical translation of a hand-held optical imager with automated coregistration facilities toward 3D tomography. Studies were performed ***in vivo*** with healthy female volunteers. A spherical target filled with a fluorescent contrast agent was placed superficially underneath the breast tissue to represent a tumor. Images were collected and coregistered using the hand-held imager. The data from the coregistered image was used to generate a 3D image of the target within the breast tissue. The results show for the first time the feasibility of performing 3D tomography in human breast tissue using a hand-held optical imager.

15. SUBJECT TERMS

Diffuse optical imaging, near-infrared, breast cancer, hand-held device, coregistration, in-vivo

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A Novel Hand-Held Optical Imager with real-Time Coregistration Facilities toward Diagnostic Mammography

Annual Report (Year 2, Jan 2010-Dec 2010)

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Grant No. BC083282
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INTRODUCTION

Optical imaging using near-infrared (NIR) light is an emerging technique toward non-invasive breast cancer diagnosis. Hand-held based optical imaging devices are currently developed toward clinical translation of the technology.[1] However, the NIR devices developed to date have not attempted three-dimensional (3D) tomography since they are not able to accurately coregister the image to the geometry of the object. ***The overall goal of the research is to implement and test a novel hand-held based optical imager with capabilities of automated coregistration on any tissue curvature for real-time surface imaging and 3D tomographic analysis, on tissue phantoms and in vivo with human subjects.*** The purpose for this research is to translate the device to the clinical setting for breast cancer imaging. The scope of the research involves experimental studies on tissue phantoms and *in vitro*, and *in vivo* studies with normal human subjects prior to clinical studies with breast cancer patients.

BODY

The tasks to be completed were outlined in the statement of work as 3 specific aims:

Specific Aim# 1: Demonstrate imaging and 3-D tomography using hand-held probe on different curved tissue phantoms.

Proposed Tasks:

(a) Modify probe design to achieve uniform source intensity.

(b) Perform experiments using the hand-held probe in the curved position on curved tissue phantoms.

Work Completed to Date:

The work for the two tasks described in this aim was performed during the first year of the grant and described in the 2009 annual report.

Specific Aim # 2: Implement 3-D automated co-registration using acoustic-based tracking system in order to perform real-time in-vivo optical imaging.

Proposed Tasks:

(a) Implement a 3D motion tracking device in order to randomly track the movement of the hand-held probe.

(b) Adapt and improve 3D reconstruction tools for optical tomography studies.

Work Completed to Date:

(a) Work for task A was completed during the first year of the grant and described in the 2009 annual report.

(b) The procedure developed herein for performing 3D tomography *in vivo* in order to reconstruct a target within the breast tissue geometry of a human subject involves ten major steps. Step 1: Acquire the coregistered image of optical intensity data from the breast tissue. Step 2: Use the 3D surface geometry from the 3D scanner to generate a 3D volume. Step 3: Generate a 3D tetrahedral volume mesh and corresponding triangular surface (or boundary) mesh for the volume breast geometry. Step 4: Determine the nodes and coordinates of the breast mesh that correspond to the source and detector positions in the coregistered probe location. The positional information of the coregistered probe location was used to find the closest nodes in the unstructured breast mesh to each source and detector in the probe, and the coordinates of those nodes were assigned as the coordinates of the sources and detectors. The procedure developed for performing this step ensures that the source and detector positions assigned to the mesh correspond to the data collected with the probe and coregistered to the tissue during live imaging. Step 5: Convert text files and source/detector positional information into data files that will be used in the reconstruction code. Step 6: Acquire the optical intensity data for each detector position in the 3D breast mesh from the coregistered image data. A code was written in MATLAB to extract the optical intensity data from the coregistered mesh at the detector nodes and generate a data file containing the coordinates of the detector nodes and the corresponding intensity values from the breast data. Step 7: Use the intensity data acquired from Step 6 to generate the data files used in the AEKF algorithm. These data files contain the AC, DC, phase, and modulation depth information (or DC only for CW data) along with the optical properties of the background tissue. In this case, average optical property values of human breast tissue acquired from the literature[2] were used in the reconstruction. Step 8: Perform 3D reconstruction using a computationally efficient version of the AEKF based algorithm to reconstruct the absorption coefficient due to the fluorophore (μ_{axf}) within the 3D discretized geometry of the breast tissue. Given the estimation of measurement error covariance R, model error covariance Q, and parameter error covariance P, the AEKF algorithm recursively minimizes the variance of the parameter error, in this case the $\mu_{axf.}$ The variances of the means of five repeated experimental measurements from each detector point were used to estimate the measurement error covariance R. The model error covariance Q was empirically chosen to be one fourth of the measurement error covariance R.[3] The R and Q were used in the

reconstruction to weight the updates at each iteration. The parameter error covariance *P* (the error in the unknown spatially distributed parameter values μ_{axf}) was used to damp into the inversion for better convergence. When the root mean square output error (RMSE) was less than 1% or the total number of iterations exceeded 50, the reconstruction was assumed to have converged. The reconstruction parameter μ_{axf} was set at an arbitrary initial guess of 0.003 cm^{-1}. The resulting 3D μ_{axf} distribution was plotted in Tecplot.

Figure 1 shows the experimental result of the image reconstructions plotted in Tecplot. Figure 1A shows the 3D tetrahedral unstructured mesh of the scanned breast tissue geometry and Figure 1B shows the reconstructed optical property (i.e. recovered absorption coefficient due to the fluorophore as a series of contour slices in the x-plane. The slices are plotted in profile view to show their location within the tissue geometry (in the breast tissue region only). Individual detailed slices are shown in frontal view in Figure 2.

The coronal slices in Figure 2 begin at the tissue surface close to the central (nipple) region and progress depth-wise toward the chest wall. The initial slices at depths less than 1.0 cm from the tissue surface at the nipple region (slices 1-3) show signal (the recovered absorption coefficient due to the fluorophore, μ_{axf}) from the 2D target location. At a depth of 1.0 cm and greater (slices 4-12), additional signal appears to the left side of the breast tissue away from the true target location at 6 o'clock position.

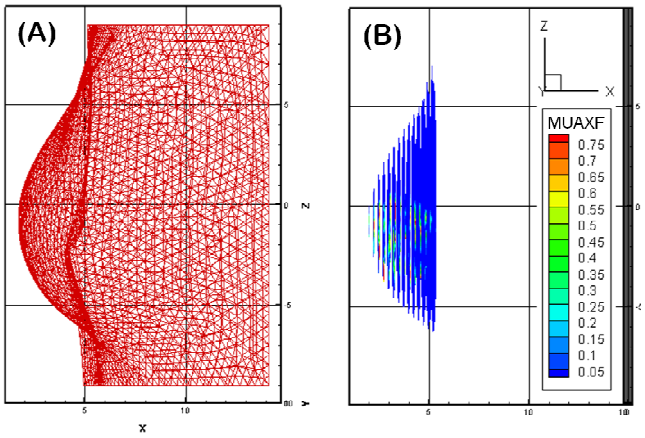

Figure 1. 3D reconstruction result using the coregistered experimental data from case #1 (section 3.1). (A) Plot of the 3D tetrahedral unstructured mesh used in the reconstruction. (B) The reconstructed parameter, absorption coefficient due to the fluorophore, μ_{axf} as a series of contour slices in the x-plane for the in vivo experimental CW-imaging. The slices are plotted in profile view to show their location within the tissue geometry (in the breast tissue region only). Individual detailed slices are shown in frontal view in Figure 2.

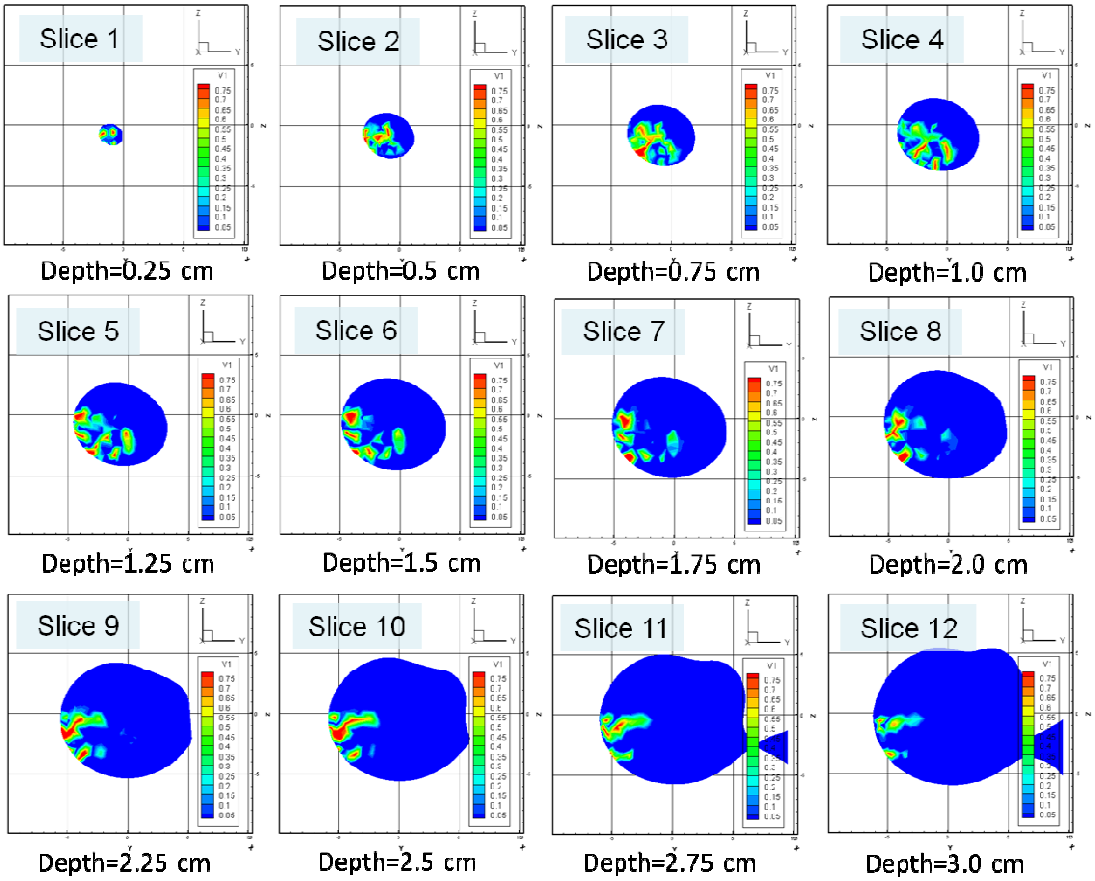

Figure 2. Contour slices of the reconstructed parameter, μaxf in the x-plane at 0.25 cm intervals, for the same reconstruction case shown in Figure 1. The contour slices begin at the tissue surface at the nipple region and slice depth is indicated as depth from the tissue surface at the center (nipple) region.

Figure 3 shows slices of the reconstructed parameter in y-plane representing the sagittal view. Slice 4 in the center gives the sagittal slice at the y=0 location which is the central part of the tissue (the slice at the nipple region). The other slices represent the locations in 0.25 cm increments to the left or towards the 9 o'clock direction (slices 1-3) and right or towards the 3 o' clock direction (slices 5-7) of the center. The images show that within this central region, there is a maximum signal intensity at the central location of the tissue which corresponds to the 6 o'clock position of the fluorescent target, and the signal diminishes in either direction away from the center.

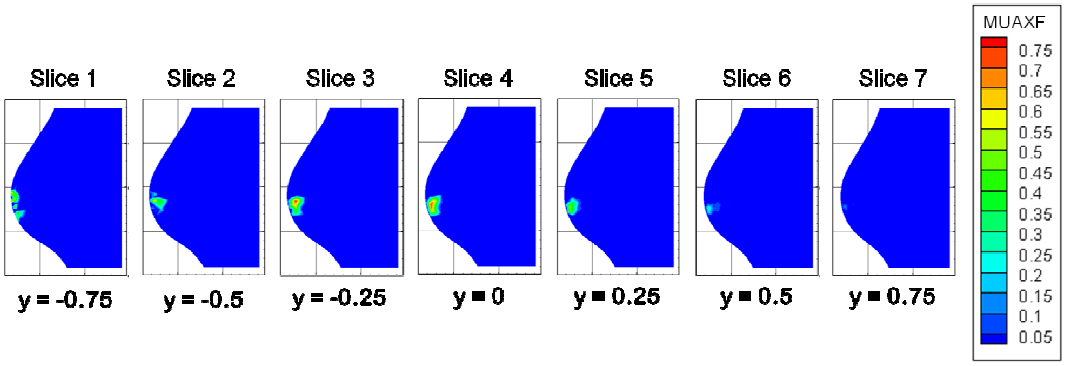

Figure 3. Contour slices of the reconstructed parameter, μaxf in the y-plane at 0.25 cm intervals, for the same reconstruction case shown in Figure 6. Slice 4 shows the central (nipple) region of the tissue which contains the true target location. The signal in highest in slice 4 and then lessens as the slices move away from center in both directions.

<u>Specific Aim # 3</u>: Perform feasibility in-vivo studies using diffuse optical imaging on normal subjects to demonstrate real-time co-registered imaging.

<u>Proposed Tasks</u>:

(a) Perform *in-vivo* studies with ~5 normal human subjects at Florida International University.

(b) Implement the tracking system to obtain real-time surface images of the human breast tissues using the hand-held optical imager.

<u>Work Completed to Date</u>:

(a) Healthy female human subjects were recruited for the study which was approved by the FIU Institutional Review Board. After the 3D scan of the tissue geometry was acquired, the subject was seated an upright position in the imaging room. Spherical target(s) of 0.23-0.45 cm^3 volume filled with 1 μM indocyanine green were superficially placed underneath the flap of the breast tissue at different locations (the 6 o'clock position is shown in Figure 4). The probe was placed in full contact with the breast tissue and CW images of fluorescence intensity were collected and automatically coregistered to the tissue geometry. A subtraction-based post-processing technique was used to eliminate excitation leakage for each image.

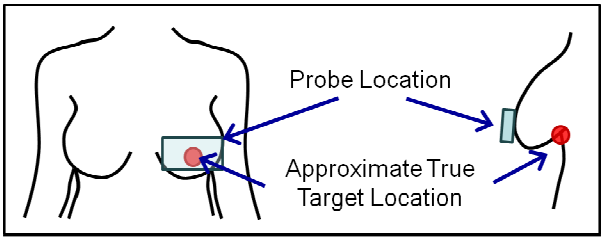

Figure 4. Schematic showing location of target placed superficially at the 6 o'clock position underneath the breast tissue and location of probe during imaging.

A commercially available handheld 3D scanner was employed to acquire the breast tissue geometry. Use of the scanner on human subjects was approved by the FIU Institutional Review Board. A motorized system was implemented with the scanner to automatically acquire the scan without requiring an operator to hold the scanner. This method was designed to enable the scanning procedure to be independent of the operator as well as to allow more privacy for the subject since the scanner would be operated by computer from outside a curtained room. Each scan was composed of a series of four sweeps of the scanner which covered both sides of the breast tissue as well as part of the chest wall and ribcage area. The acquired geometry was displayed by the scanner software (Figure 5A) and then exported as a .MAT file. The geometry was then discretized using MATLAB software developed in house, and loaded into the coregistration software (Figure 5B).

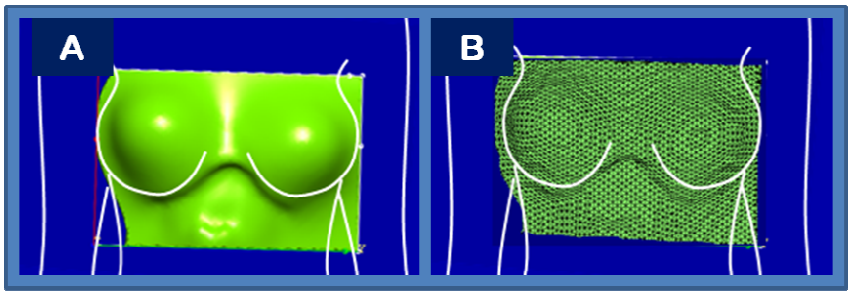

Figure 5. (A) Scanned surface breast tissue geometry. (B) Discretized mesh of breast tissue surface geometry.

Coregistered imaging is required in order to perform 3D tomography since the 2D images (contour plots of fluorescent intensity data acquired using the hand-held optical imager) must be coregistered to the appropriate probe location on the tissue surface. In coregistered imaging, the position and orientation of the probe is tracked with respect to the tissue or phantom surface being imaged. This tracked 3D positional information is then used to accurately position the acquired optical images onto the tissue geometry.

Coregistration was carried out as a three-step process using MATLAB/LabVIEW software developed in house[4]: (1) a real-time tracking system was used to find the probe location in 3D with respect to the tissue; (2) a real-time 2D surface contour optical image was acquired at the probe location; (3) the 3D probe location and 2D optical image were coregistered onto a discretized phantom mesh. The 3-step process is automated to enable fast 2D coregistered imaging (~35 seconds per image).

The automated coregistered imaging process was previously validated in human subjects. The probe was placed at reference points of known coordinates and the distance off between the true and measured position was calculated for each probe location. The average distance off was ~ 1cm. The error can be attributed to instrumentation error such as fluctuation in the tracked position of the probe, and human error such as hand

movement of the operator. Currently the tracking system and imaging set-up is being modified to improve the accuracy of the tracked probe location.

Figure 6 shows results for coregistered imaging studies with a normal subject. A spherical target filled with 1 μM ICG was placed underneath the flap of the breast tissue and fluorescence intensity images were collected and automatically coregistered using the positional tracking system. Figure 6A shows the position of the probe and the discretized geometry relative to the subject.

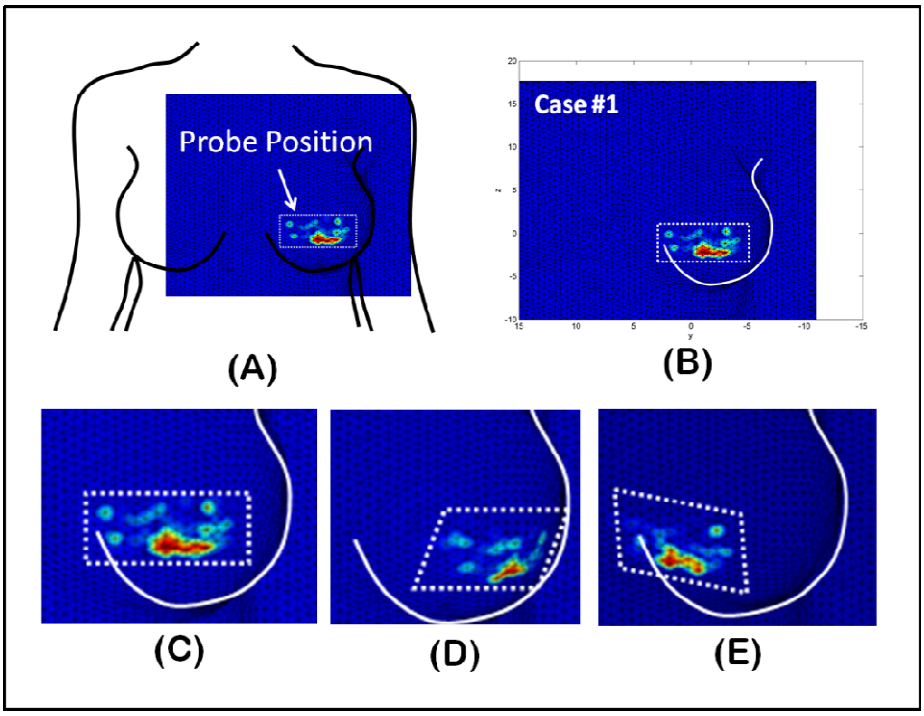

Figure 6. Coregistered images of fluorescence intensity data collected form a normal subject with an ICG-filled target using the initial set-up (subject seated in upright position). (A) Location of probe and image relative to the subject. (B) Case#1 image: 0.45 cm3 target at the 6 o'clock position. (C) Zoomed image of Case #1. (D) Case #2 image: 0.45 cm3 target at the 4 o'clock position. (E) Case #3 image: 0.23 cm3 target at the 8 o'clock position. All targets contain 1 μM indocyanine green.

Figure 6B shows the resulting coregistered image for case #1 where a 0.45 cm^3 target was placed at the 6 o'clock position. A zoomed image of the same result is shown in Figure 3C. Figures 3D and 3E show zoomed images of the results for cases #2 (0.45 cm^3 target at the 8 o'clock position) and #3 (0.23 cm^3 target at the 4 o'clock position) respectively. The results show that a 0.23-0.45 cm^3 fluorescent target was detected through ~2.5 cm of human breast tissue and coregistered to the appropriate location on the tissue geometry.

(b) In order to minimize the movement of the subject and the breast tissue, the imaging set-up was modified such that the subject lay in a reclined position. A massage chair

capable of reclining 45-90º with arm rests was acquired for the imaging studies (Figure 7). The subjects rested in supine position on the chair with the back reclined at 45º and arms resting at the sides or on the armrests. This position was chosen such that it would be reclined enough to minimize movement of the subject (as opposed to the upright position with no armrests in the initial set-up which allowed movement of the subject) as well as maintain line-of-sight between the probe and the tracker which would be inhibited if the chair was reclined to greater angles. In order to acquire the 3D geometry with the subject in the reclined position, the Fastscan was taken back as a hand-held scanner and used to scan the tissue by hand (the motorized system will be used in future applications described in the last chapter).

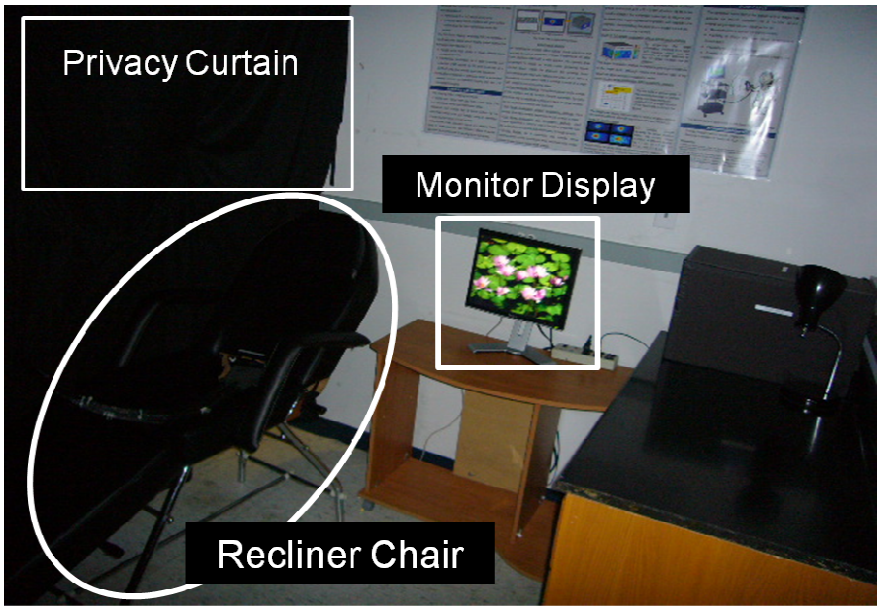

Figure 7. Modified human subject imaging set-up. Subject lies supine in recliner chair (45º) during acquisition of tissue geometry with 3D scanner and imaging using handheld imager.

Figure 8 shows the 3D scanned geometry of a normal human subject using the modified set-up where the subject was lying in supine position in a recliner chair at a 45º angle. The reclined position caused the tissue to flatten against the ribcage in order to minimize deformation of the tissue during imaging.

The imaging process using the modified set-up is shown in Figure 9, where the imaging room is closed off from the instrumentation room by a curtain and only the probe is visible in the room. The probe was placed against the breast tissue while the location was recorded by the acoustic tracker and the images were automatically coregistered at the probe location relative to the tissue geometry. The resulting images were immediately displayed on a monitor in the imaging room that was linked to the computer operated from the instrumentation room.

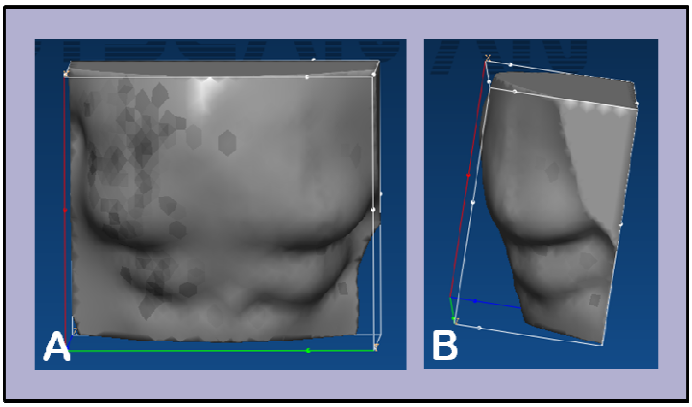

Figure 8. Geometry acquired using the modified imaging set-up with normal subject lying supine in recliner chair with 45º angle. (A) Frontal view. (B) Side view.

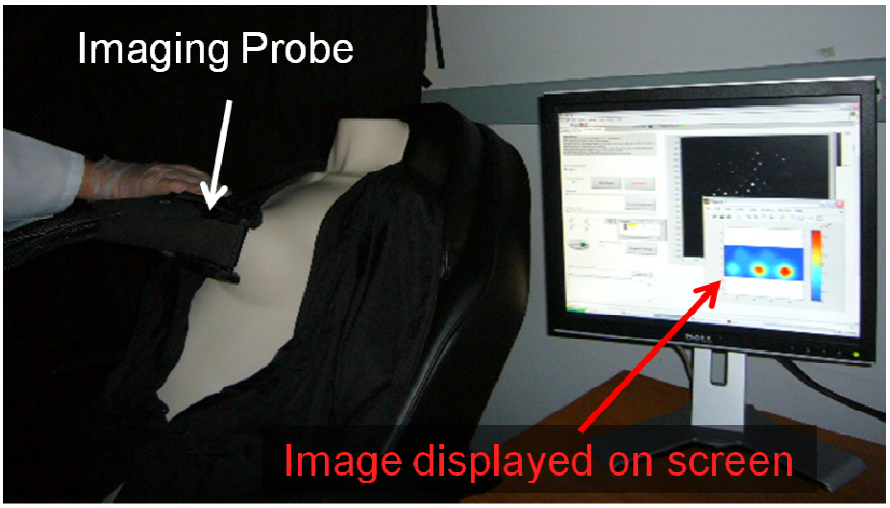

Figure 9. Modified imaging set-up. The subject lies in supine position in recliner chair while breast tissue is imaged using hand-held optical imager. Mannequin shown for demonstration only.

Figure 10 shows automated coregistered images from a normal human subject using the modified imaging set-up with the acoustic tracker. The geometry was rotated to a 45º angle over the y-axis in the coregistration software to correspond to the 45º reclined position of the subject. A default image was used in this study since the purpose of the study was to demonstrate coregistered imaging using the modified approach and not to detect a target. The probe location was coregistered to the tissue at two different locations: the first location was centered over the breast tissue with the bottom of the probe positioned 2 cm beneath the nipple region (Figure 10A-C) and the second location was above the breast in the chest wall region with the bottom of the probe positioned 3 cm above the nipple region (Figure 10D-E).

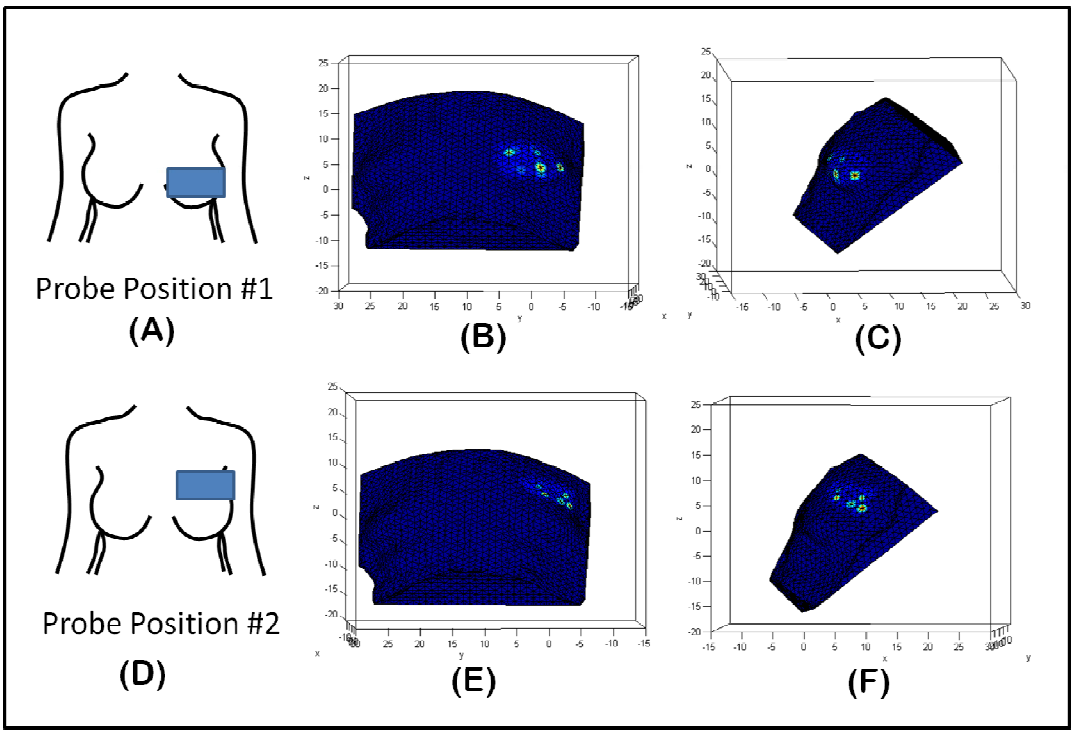

Figure 10. Automated coregistered images in normal subject (no target) using modified imaging set-up. (A) Probe position #1. (B) Frontal view of coregistered image at probe position #1. (C) Side view of coregistered image at probe position #1. (D) Probe position #2. (E) Frontal view of coregistered image at probe position #2. (F) Side view of coregistered image at probe position #2.

Problems were encountered with the acoustic based tracking system and it was determined that an alternative tracking system would need to be incorporated. A master's student in the lab took over the task of testing different tracking systems to use in place of the acoustic based tracker. In the meantime, manual coregistered imaging was performed in human subjects by measuring and marking the probe locations on the tissue.

Figure 11 shows results from absorption-based studies in a normal subject with a 0.45 cm^3 target filled with 0.08% India ink (absorbing contrast agent) placed underneath the flap of the breast tissue at the 6 o' clock position. For this study, the probe position was measured on the breast tissue and marked using surgical tape. The image was then manually coregistered at the measured position using post-processing coregistration software. Figure 11A shows the location of the probe relative to the subject. Figure 11B shows the probe location placed manually in the post-process coregistration software, and Figure 11C shows the resulting coregistered image. It can be seen that the target is detected as a lower intensity (blue) signal indicating higher absorption at the location of the target. A background image was also collected (without target) and subtracted to eliminate background noise.

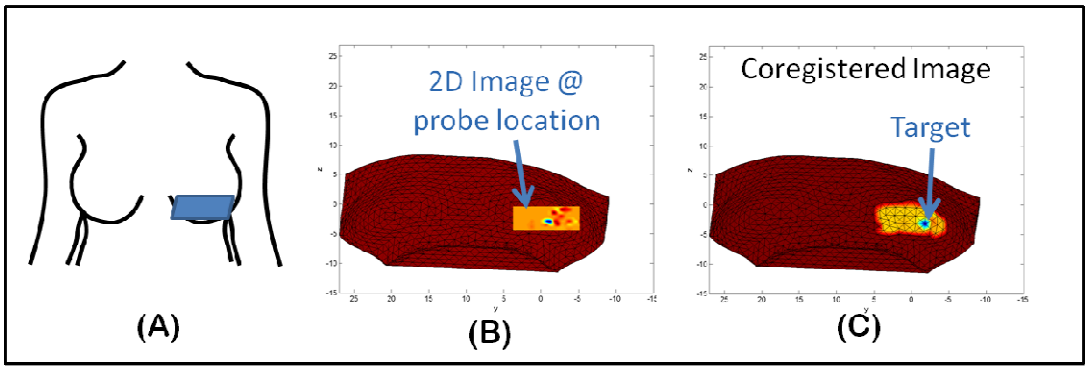

Figure 11. Manually coregistered images from normal subject with 0.45 cm3 target with 0.08% India ink placed under the breast tissue at the 6 o'clock position.

Figure 12 shows the results from a similar study where a target of lower concentration (0.02% India ink) was placed underneath the breast tissue at the 6 o' clock position. Figure 12A shows the location of the probe relative to the subject. Figure 12B shows the probe location placed manually in the post-process coregistration software, and Figure 12C shows the resulting coregistered image. The resulting contrast is lower due to the lower concentration of the absorbing agent, but the lower signal (blue) from the target can be seen at the target location in the 2D image (Figure 12B) and the coregistered image (Figure 12C).

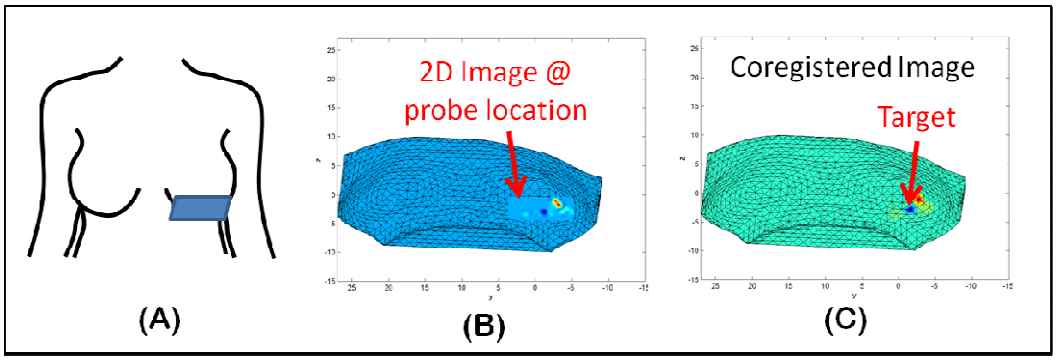

Figure 12. Manually coregistered images from normal subject with 0.45 cm3 target with 0.02% India ink placed under the breast tissue at the 6 o'clock position.

Training Plan

Clinical Studies

The P.I. continued meetings with Dr. Richard Kiszonas (clinical mentor) to discuss breast imaging with human subjects and challenges that are encountered.

Mentoring

During Year 2, the P.I. mentored two undergraduate students in experimental studies with phantoms and human subjects, and one masters student in human subject studies.

Doctoral Dissertation

The P.I. has completed the experimental studies for the research and has begun writing the doctoral dissertation.

KEY RESEARCH ACCOMPLISHMENTS

- Adapted 3D reconstruction tools for 3D tomographic imaging in vivo. **(Specific Aim #2)**
- Demonstrated automated coregistered imaging in 2-3 normal human subjects. **(Specific Aim #3).**
- Performed manual coregistered imaging in human subjects using system of marking known probe locations on tissue.
- Demonstrated feasibility of performing 3D tomography using coresgistered image from a human subject.

REPORTABLE OUTCOMES

Peer-reviewed Journal Publications

(1) **S.J. Erickson,** S.L. Martinez, J. Gonzalez, L. Caldera, and A. Godavarty. "Improved detection limits using a hand-held optical imager with coregistration capabilities," *Biomedical Optics Express* 1, 126-134 (2010).

(2) **S.J. Erickson**, J. Ge, A. Sanchez, and A. Godavarty. "Two-dimensional fast surface imaging using a hand-held optical device: in-vitro and in-vivo fluorescence studies," *Translational Oncology* 3(1): 16-22 (2010).

(3) J. Ge , **S.J. Erickson**, and A. Godavarty, "Multi-projection fluorescence optical tomography using a handheld-probe-based optical imager: phantom studies," *Applied Optics* 49, 4343-4354 (2010)

(4) S. Regalado, **S.J. Erickson**, B. Zhu, J. Ge, and A. Godavarty. "Automated coregistered imaging using a hand-held probe-based optical imager," *Review of Scientific Instruments* 81: 023702 (2010).

National Conference Proceedings

(1) **S.J. Erickson**, S. Martinez, J. Gozalez, M. Roman, A. Nunez, and A. Godavarty. "3D tomographic breast imaging using a hand-held optical imager," SPIE Photonics West, San Francisco, CA, Jan. 22-27, 2011.

(2) J. Gonzales, J. DeCerce, S. Martinez, **S.J. Erickson**, and A. Godavarty, "Simultaneous bilateral breast imaging using a novel handheld optical device," SPIE Photonics West BiOS, San Francisco, CA, January 22-27, 2011.

(3) **S.J. Erickson**, S. Martinez, J. Gonzalez, L. Caldera, and A. Godavarty. "Non-invasive Diagnostic Breast Imaging using a Hand-held Optical Imager," Proceedings of the 14th World Multi-Conference on Systems, Cybernetics and Informatics, 2010.

(4) **S.J. Erickson**, S. Martinez, L. Caldera, and A. Godavarty, "Improved Detection Limits Using a Hand-Held Optical Imager with Coregistration Capabilities," in Biomedical Optics, OSA Technical Digest (Optical Society of America, 2010), paper BTuD43.

(5) S. Martinez, J. DeCerce, J. Gonzalez, **S.J. Erickson**, and A. Godavarty, "Assessment of Tracking Devices towards Accurate Coregistration in a Hand-Held Optical Imager," in Biomedical Optics, OSA Technical Digest (Optical Society of America, 2010), paper BTuD58.

(6) **S.J. Erickson**, S. Martinez, J. DeCerce, A. Romero, L. Caldera, A. Godavarty. "Fast coregistered imaging in vivo using a hand-held optical imager," Advanced Biomedical and Clinical Diagnostic Systems VIII. Edited by Vo-Dinh, Tuan; Grundfest, Warren S.; Mahadevan-Jansen, Anita. Proceedings of the SPIE, Volume 7555, pp. 75550P-75550P-6 (2010).

Awards

(1) **Session Best Paper Award**, 14th World Multi-Conference on Systems, Cybernetics and Informatics, Orlando, FL, 2010

(2) **1st Place Engineering Paper Competition Award**, Scholarly Forum, Florida International University, Miami, FL, 2010

Funding Received

A post-doctoral fellowship grant application was submitted to the American Cancer Society and received a score of "Outstanding", but fell below the pay-line. The application was placed in the "Pay-if-Additional-Funds-Become-Available" category. The application was also resubmitted for the next grant cycle.

CONCLUSION

The objectives outlined in the statement of work that have been completed in the past year are Specific Aim #2 (task B) and Specific Aim #3. The major outcomes from these tasks are: (i) demonstration of coregistered imaging in vivo in 2-3 healthy female subjects, (ii) manual coregistered imaging in human subjects using modified imaging set-up, and (iii) feasibility of performing 3D tomography in vivo using coregistered images from human subjects. The results obtained were published in the peer-reviewed journals *Biomedical Optics Express, Translational Oncology* and *Review of Scientific Instruments* and presented at the national meetings *SPIE Photonics West* and *Optical Society of America*.

The results from these tasks demonstrate the ability of the hand-held device to perform automated coregistered imaging in vivo on complex breast tissue geometries. A fluorescent target was detected *in vivo* through human breast tissue and coregistered at the appropriate tissue location which demonstrates the potential of the device to detect a tumor in the clinical setting. The acoustic tracking was found to be inadequate and alternate tracking systems are currently being explored. The feasibility of performing 3D tomography in human breast tissue was demonstrated for the first time using a near-infrared hand-held optical imaging device.

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